

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Christos Zouboulis
Serial No. : 09/920,392
For : SEBOCYTES, SEBOCYTE – CELL LINE AND USES
THEREOF
Filed: : August 01, 2001
Examiner : Leon B. Lankford, Jr.
Art Unit : 1651

DECLARATION OF CHRISTOS ZOUBOULIS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Christos Zouboulis, hereby declare and state as follows:

1. I am Director of the Departments of Dermatology and Immunology of the Dessau Medical Center, Dessau, Germany; and Head of the Research Group on Biogerontology, Dermatopharmacology and Dermatoendocrinology at the Institute of Clinical Pharmacology and Toxicology, Charite University Medical Center, Berlin, Germany. Attached hereto as Exhibit A is a copy of my Curriculum Vitae.

2. I am the sole inventor of the above-captioned application ("present application"), and I am informed of the prosecution of the present application, particularly of the pending March 21, 2006 office action. I have personal knowledge of the facts stated herein.

3. My patent discloses and claims, among other things, sebocytes derived from a human immortalized *in vitro* and a human sebocyte cell line.

4. Prior to my invention of the immortalized sebocyte and the immortalized sebocyte cell line disclosed in the present application, numerous scientific groups and companies tried, but failed, to obtain immortalized sebocytes.

4. In the 1980's I began work on the isolation and *in vitro* cultivation of human sebocytes and published this work in the Journal of Investigational Dermatology, vol. 93, pages 315-321 (1989).

5. I subsequently determined that an immortalized cell line of human sebocytes should be developed to provide sufficient viable cells to advance the science of acne and other skin diseases and I began efforts to do so utilizing the techniques set forth in a pioneering paper by M. Blumenberg and his colleagues in the Journal of Investigational Dermatology, vol. 97, pages 969-973 (1991) on various techniques for the immortalization of human epidermal keratinocytes which are a class of cells fairly closely related to sebocytes. It was my expectation at the time that the techniques outlined in this article could be successfully applied to sebocytes.

6. Initially my efforts by all of these techniques failed to yield any immortalized cells. Subsequently I was able to immortalize some cells but only using the lipofection technique. These cells, however, failed to display any of the key characteristics of sebocyte, such as the synthesis of lipids or response to retinoids.

7. I then began an intensive screening program attempting to immortalize skin cells drawn from many body sites and many different types of individuals. I had a particular interest in older individuals and particularly facial skin cells from such individuals because own data became available in early 1995 that such cells did not proliferate or did not proliferate well. I took this feature as an indication that mature cells, for example from individuals 50 years or older, might yield immortalized sebocytes.

8. In an experiment with the facial cells of an 87 year old woman, cells were obtained after attempted immortalization via lipofection which appeared not to grow at all. However, I had the cells kept under observation for a period of approximately three months and ultimately observed some cells which were growing. On analysis, these cells proved to be immortalized sebocytes; they produced lipids and the SV 40 T cell antigen characteristic of the immortalizing agent. This work was then published in the Journal of Investigational Dermatology, vol. 113, pages 1011-1020 (1999) and described in the present patent application.

9. Although I am quite active in the field of sebocyte technology and try to keep abreast of the relevant literature. I am not aware of anyone independently developing immortal sebocytes. I am aware of the work of a Dr. Thiboutot and her colleagues reported in the Journal of Investigational Dermatology, vol 120, pages 905-914 (2003), in which the procedures outlined in my 1999 article were successfully followed.

10. News of my success in achieving immortalized sebocytes and a sebocyte cell line generated considerable interest in the pharmaceutical and cosmetic industry, as well as the scientific community.

11 I have licensed my immortalized sebocytes to fourteen pharmaceutical and cosmetic companies, eight of which have annual sales in excess of \$2 billion, nine of which have annual sales in excess of \$500 million and eleven of which have annual sales in excess of \$100 million.

12. Upon request, I have provided the opportunity to receive samples of my immortalized sebocytes to sixty eight research laboratories worldwide. From this, twenty nine original manuscripts reporting on research utilizing my immortalized sebocytes have been published, and five more have been accepted for publication.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

August 18, 2006

Date



Christos Zouboulis

Exhibit A

Prof. Dr. med. Christos C. Zouboulis

August 2006

Present Positions

Director, Departments of Dermatology and Immunology, Dessau Medical Center, Auenweg 38,
06847 Dessau, Germany
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dessau.de](mailto:christos.zouboulis@klinikum-dessau.de)

Head, Research Group on Biogerontology, Dermatopharmacology and Dermato-Endocrinology,
Institute of Clinical Pharmacology and Toxicology, Charité Universitätsmedizin Berlin, Campus
Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany
Tel.: 030-84452765, Fax: 030-84452766, E-mail: christos.zouboulis@charite.de

Education

Medical School, National University of Athens (1978-84)

Department of Political Sciences, National University of Athens (1984-87)

Previous Clinical Appointments

Preventive Medicine Resident, 251 Air Force General Hospital, Athens (1985)

Internal Medicine Resident, 251 Air Force General Hospital, Athens (1985-87)

Dermatology and Venereology Resident, Department of Dermatology, University Medical Center
Steglitz, Freie Universität Berlin (1988-92)

Allergy Resident, Department of Dermatology, University Medical Center Steglitz, Freie
Universität Berlin (1990-92)

Senior Registrar, Department of Dermatology, University Medical Center Benjamin Franklin, Freie
Universität Berlin (1994-2000)

Vice-Chair, Department of Dermatology, Charité Universitätsmedizin Berlin, Campus Benjamin
Franklin (2000-04)

Director, Outpatient Division, Department of Dermatology, Charité Universitätsmedizin Berlin,
Campus Benjamin Franklin (2000-04)

Director, Outpatient Division, Department of Dermatology, Charité Universitätsmedizin Berlin,
Campus Charité Mitte (2004-05)

Previous Research Appointments

Research Fellow, Department of Dermatology, University Medical Center Steglitz, Freie Universität
Berlin (1987-88)

Research Fellow, Department of Dermatology, University of Michigan, Ann Arbor, USA (1993)

Research Fellow, Department of Dermatology, The Cleveland Clinic Foundation, Cleveland, USA
(1993)

Research Fellow, Department of Dermatology, Massachusetts General Hospital, Harvard Medical
School, Boston, USA (1994)

Academic Appointments, Degrees and Diplomas

M.D., University of Athens (1984)

Fellow, Department of Nursery, Medical School, National University of Athens (1986-87)

Dr. med., Medical School, The Free University of Berlin (1988)

Diploma in Dermatology and Venereology, Berlin Medical Association (1992)

Lecturer and faculty member, Department of Dermatology, Medical School, Freie Universität Berlin
(1992-94)

Diploma in Dermatology and Venereology, Greek Ministry of Health and Welfare (1993)

Diploma in Allergology, Berlin Medical Association (1993)
Senior lecturer and faculty member, Department of Dermatology, Medical School, Freie Universitaet Berlin (1994-95)
Ass. Professor in Dermatology and Venereology, Medical School, Freie Universitaet Berlin (1995)
Professor, Freie Universitaet Berlin (2000)

Major Research Interests

Biogerontology - Dermato-Endocrinology - Dermato-Pharmacology – Molecular Cell Biology and Biotechnology of the Skin / Physiology and Pathophysiology of the Sebaceous Gland / Acne - Rosacea – Adamantiades-Behçet's Disease – Malignant Atrophic Papulosis – Hidradenitis suppurativa - Keloids / Androgens, Antiandrogens – Neuropeptides – Retinoids– Cryosurgery

Major Research Projects

Co-ordinator of the EP "Genetic Etiology of Human Longevity" of the National Genome Research Network (NGFN-2) (2004-2007)
Coordinator of the BMBF-supported German-Greek cooperation project "Molecular mechanisms of degradation of the cutaneous elastic tissue in aged individuals" (2004-05)
Member of the Steering Committee of the European Union FP6 project LSH-2003-2.1.4-3 "Coordination and Consolidation of European Biogerontology: en route towards formation of a European College of Biogerontology" (2005-2008)
Member the BMBF RNA Technologies Network with the project "Prevention of Skin Aging through sRNA" (2005-2006)
Member of the DFG Graduate College "Hormonal Regulation of Energy Metabolism, Body Weight and Growth" with the project "Hormones and molecular mechanisms of intrinsic ageing" (2005-2008)

Honors and Awards

Major awards

"Skin Cancer Prize" for the best article August 1990-December 1991, Journal „Skin Cancer" (1992)
"Oskar Gans Major Prize" for Dermatological Research, German Dermatological Society (DDG) (1993)
Visiting Professor, Department of Dermatology, The Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, USA (1993)
European Academy of Dermatology and Venereology Dermatology Research Fellowship (1997)
"Felix Wankel Animal Protection Research Prize", Faculty of Veterinary Medicine, Ludwig Maximilians University of Munich (2000)
"Beauty Care Prize" for excellent Dermatological Research, German Study Group Dermatological Cosmetology (2000)
"Beauty Care Prize" for excellent Dermatological Research, German Study Group Dermatological Cosmetology (2002)
"Geroulanos Prize" for History of Medicine, Hellenic Medical Association (2003)
"Dionysios Ikkos Lectureship", Hellenic Association of Endocrinology and Metabolism (2005)
"Paul Gerson Unna Prize" for Research in the area of the Innate Immunity, German Dermatological Society (DDG) (2005)
"Liérac Research Award" for Research in the area of Skin Ageing, Liérac Inc. and French Dermatological Society (2005)

Other prizes

Scholarship for excellence in medical studies, The State Scholarships' Foundation of Greece (1980-84)
Summer-Scholarship for medical studies at the University of Turku, Finland, International Federation of Medical Students Associations (IFMSA) (1982)

Summer-Scholarship for medical studies at the University of Rotterdam, Holland, International Federation of Medical Students Associations (IFMSA) (1984)
Scholarship for postdoctorate medical education in Dermatology, The Department of Dermatology, University Medical Center Steglitz, The Free University of Berlin and the Senate of Berlin (West) (1988)
Poster prize for experimental research, 1st Scientific Week of the University Medical Center Steglitz, The Free University of Berlin (1990)
1st poster prize, IIIRD International Dermatology Symposium (IDS) Berlin (1991)
Poster prize, 2nd Congress of the European Academy of Dermatology and Venereology, Athens (1991)
Poster prize, 5th Scientific Week of the University Medical Center Benjamin Franklin, The Free University of Berlin (1994)
1st experimental poster prize, 38th Congress of the German Dermatological Society (DDG), Berlin (1995)
3rd clinical poster prize, 38th Congress of the German Dermatological Society (DDG), Berlin (1995)
1st prize for oral or poster presentation, 2nd Cypriot-Greek Dermatological Congress, Larnaca, Cyprus (1997)
Poster prize, 7th Congress of the European Academy of Dermatology and Venereology, Nice, France (1998)
1st lecture prize, 42nd Congress of the German Dermatological Society (DDG), Berlin (2003)

Prizes of coworkers

Dr. S. Kienbaum, Thesis prize of the German-Turkish Medical Society (1995)
Dr. A. Paraskevaidis, experimental poster prize, IV. International Dermatology Symposium Berlin (1997)
Dr. K. Seiffert, travel fellowship, International Investigative Dermatology'98 Congress (1998)
H. Seltmann, poster prize, 40th Congress of the German Dermatological Society, Hamburg (1999)
Dr. M. Tsukada, travel fellowship, Congress of the European Retinoid Research Group (1999)
Dr. A. Dalkowski, Alexis Carrel Prize for Cryobiology, Cryomedicine, Cryosurgery and Biotechnology of the International Institute for Refrigeration (1999)
H. Seltmann, poster prize, 9th Austrian Congress of Replacement and Complementary Methods to Animal Research, Linz, Austria (2000)
Dr. M. Tsukada, Allergan Annual Award for Basic Science (2000)
Y. Adler, best clinical case report, 113th Meeting of the Berlin Dermatological Society, Potsdam (2000)
J.R. Turnbull, 2nd best clinical case report, 115th Meeting of the Berlin Dermatological Society, Berlin (2002)
K. Orlowski, Charité Thesis Scholarship (2003-04)
M.F. Steinhoff, best clinical case report, 117th Meeting of the Berlin Dermatological Society, Berlin (2004)
N. Papoutsis, Charité Thesis Scholarship (2004-05)
R. Ganceviciene, Berlin Foundation of Dermatology Scholarship (2005)
S. Angres, Charité Thesis Scholarship (2005)
A. Theodoridis, Berlin Foundation of Dermatology Scholarship (2005-06)
Dr. E. Makrantonaki, Hermal Support Prize on Dermatology (2006)
Dr. E. Makrantonaki, William J. Cunliffe Prize (2006)

Scientific Activities

Conference organisation

IIIRD International Dermatology Symposium (IDS), Berlin (1991) - Deputy Secretary
38th Congress of the German Dermatological Society (DDG), Berlin (1995) - Deputy Secretary

- 7th International Conference on Behçet's disease, Tunis, Tunisia (1996) - Member of the scientific committee
- IVth International Dermatology Symposium Berlin „Sebaceous gland, acne and related disorders - Basic and clinical research, clinical entities and treatment“, Berlin (1997) - Secretary, member of the scientific and abstract evaluation committees
- 8th International Conference on Behçet's disease, Reggio Emilia, Italy (1998) - Member of the scientific committee
- Satellite Symposium „Sebaceous gland, sebocyte and infundibulum cultures: Models for acne and sebaceous gland research“ to the International Investigative Dermatology 98 Congress, Cologne (1998) - Local organizer and member of the scientific committee
- 9th International Conference on Behçet's disease, Seoul, Korea (2000) - Member of the scientific committee
- 3rd Teupitz Colloquium "Basic Research in Endocrine Dermatology", Teupitz (2000) – Organizer
- 1st Meeting of the Research Group "Endocrine Dermatology" of the German Society for Dermatological Research, Berlin (2002) – Organizer
- Heidelberg-Berlin Symposium „Retinoids and Vascular Disease“, Heidelberg (2002) - Co-Organiser
- 12th Annual Meeting of the Berlin Dermatological Society (2002) - Organizer
- 10th International Conference on Behçet's disease, Berlin (2002) - President
- 2nd Meeting of the Research Group "Endocrine Dermatology" of the German Society for Dermatological Research, Frankfurt/Main (2003) – Organizer
- 117th Meeting of the Berlin Dermatological Society (2004) – Organizer
- 12th Annual World Congress of Anti-Aging Medicine (2004) – Academic program committee advisor
- 1st Conference of the NGFN-2 EP Project "Genetic Etiology of Human Longevity" - Organizer
- 1st International Conference for Atrophic Malignant Papulosis (2005) - Organizer
- 1st International Conference on Hidradenitis Suppurativa (2006) – Local Organizer
- 1st European Summer School on Dermatology (2006) - Chair

Session organisation (major meetings)

- 2nd Congress of the European Academy of Dermatology and Venereology, Workshop „Cryosurgery“, Athens, Greece (1991)
- 39th Meeting of the German Dermatological Society (DDG), Workshop „Molecular biology and dermatology - An introduction“, Karlsruhe (1996)
- 19th World Congress of Dermatology, Session „Cutaneous molecular biology“, Sydney, Australia (1997)
- World Congress of Cryobiology, Session "Cryosurgery", Marseille, France (1999)
- 20th Congress of the International Society for Dermatologic Surgery, Workshop „Cryosurgery“, Athens, Greece (1999)
- 10th Congress of the European Academy of Dermatology and Venereology, Honorary Symposium for Prof. William J. Cunliffe, Munich, Germany (2001)
- 20th World Congress of Dermatology, Symposium „Acne“, Paris, France (2002)
- 11th Congress of the European Academy of Dermatology and Venereology, Workshop „Mucous Membrane Disorders“, Prague, The Czech Republic (2002)
- 42nd Meeting of the German Dermatological Society (DDG), Symposium „Acne and Rosacea“, Berlin (2003)
- 12th Congress of the European Academy of Dermatology and Venereology, Symposium „Acne“ and Symposium "William J. Cunliffe Scientific Awards", Barcelona, Spain (2003)
- 4th International Meeting of the Hair Research Societies, Seminar "Endocrinology of the Pilosebaceous Unit", Berlin (2004)
- 43rd Meeting of the German Dermatological Society (DDG), Workshop „Endocrinology“, Dresden (2005)
- 3rd Spring Symposium of the European Academy of Dermatology and Venereology, Workshop „Adamantiades-Beçet's Disease“, Sofia, Bulgaria (2005)
- IV World Congress of the International Academy of Cosmetic Dermatology - Symposium "Acne", Paris, France (2005)

14th Congress of the European Academy of Dermatology and Venereology, Symposium „Acne“, London, UK (2005)

15th Congress of the European Academy of Dermatology and Venereology, Symposium „Endocrinology of the skin“, Rhodes, Greece (2006)

Editorial activities

Dermatology - Assistant Editor (1997-)

Journal of Dermatological Treatment - Editorial Board (1998-)

Clinical and Experimental Rheumatology - Editorial Board (2002-)

The Journal of Investigative Dermatology - Associate Editor (2003-)

International Journal of Molecular Medicine – Editorial Academy (2003-)

Hellenic Dermatotomy – International Editorial Council (2004-)

APLAR Journal of Rheumatology – Editorial Board (2005-)

Aktuelle Dermatologie – Editorial Board (2006-)

Dermatologische Monatsschrift, Special issue on Cryosurgery - Guest Editor (1993)

Abstract Book of the 38th Congress of the German Dermatological Society (DDG) - Co-Editor (1995)

Dermatology, Proceedings of the IVth International Dermatology Symposium Berlin - Guest-Editor (1998)

Hormone Research, Proceedings of the 3rd Teupitzer Colloquium - Guest Editor (2000)

Journal of Skin Pharmacology and Applied Skin Physiology, Honorary Edition dedicated to the 65th Birthday of Prof. Dr. C.E. Orfanos - Guest Editor (2001)

Dermatology, Acne-Symposium, 20th World Congress of Dermatology, Paris, France - Guest-Editor (2003)

Experimental Dermatology, Supplement on Dermato-Endocrinology – Guest Editor (2004)

Aktuelle Dermatologie, 10 years Research Support Prizes of the BDG – Guest Editor (2004)

Hormones and Metabolic Research, Special issue “Endocrinology of the Skin” – Guest Editor (2005)

Journal of the Deutsche Dermatologische Gesellschaft, Special issue “Evidenced-based acne treatment” – Guest Editor (2006)

Professional Societies (Board Member)

International Study Group for Behçet's disease - Board of Directors (1993-98)

International Society of Behçet's disease - Council (1998-), Executive Committee (2000-)

European Association of Cryosurgery - Board of Directors and Founding Member (1996-2003)

International Society of Cryosurgery - Advisor to the Board (1996-98), Board of Directors (1998-)

European Acne Advisory Board – Member (2002-)

European Society of Anti-Aging Medicine (ESAAM) – Member of the Scientific Advisory Board (2004-)

Forum for the Improvement of Clinical Trials in Acne (FICTA) – Coordinator (2004-)

German Dermatological Society (DDG) Guideline Committee for Acne – Member (1997-2002)

German Dermatological Society (DDG) Acne Consensus Committee – Member (2002-), Chair (2003-)

Research Group “Endocrine Dermatology” of the German Society for Dermatological Research – Chairman (2000-2003)

Working Group Cryosurgery in Germany - Speaker for Dermatology (1997-)

Committee for Revision of the Bylaws of the European Society for Dermatological Research (ESDR) – Member (2001-2002)

German University Professor Association (DHV) Berlin - Executive Board (1997-2004), Delegate to the DHV Meeting (1998)

Berlin Dermatological Society (BDG) – Board Member (2000-2004), President (2002-2004)

William J. Cunliffe Scientific Awards – Chairman of the Executive Committee (2001-)

Work Group Group “Endocrine Dermatology” of the German Dermatological Society – Coordinator (2006-)

University Committee and Administrative Service
Executive Council, Medical School, National University of Athens (1982-84)
Ethics Committee, Medical School, The Free University of Berlin (1991-93)
Research Committee, Medical School, The Free University of Berlin (1994-2004)
Vice-Chair of the Research Support Committee, Medical School, The Free University of Berlin (1997-99)
Executive Council, Medical School, The Free University of Berlin (1996-99)
Council, The Free University of Berlin (1999-2001)
Finances Committee, Medical School, The Free University of Berlin (2001-04)
Executive Council, Charité Universitätsmedizin Berlin (2003-06)
Research Committee, Charité Universitätsmedizin Berlin (2004-06)
Committee for International Affairs, Charité Universitätsmedizin Berlin (2004-06)
Steering Committee, Transatlantic Project "Issues of Aging", Charité Universitätsmedizin Berlin (2005-)

Publications

240 peer reviewed, 29 letters and editorials, 15 books, 70 book chapters, 4 patents
Impact Factor 512, Citations 2054, Science Citation Index 4680

Invited Lectures

Over 250 invited lectures

Further Honorary Activities

Charity „Deutsches Register Morbus Adamantiades-Behçet e.V.“ – Chairman
Charity „Freunde und Förderer der Stiftung für Griechische Kultur e.V.“ – Secretary (1996-2004)
Charity „Deutscher Dermatologen Kongreß 1995 - Verein zur Förderung der Dermatologie e.V.“ –
Foundation member

Dessau, August 18, 2006



Prof. Dr. Christos C. Zouboulis